REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 1-12 were pending in this application when last examined.

Claims 1-4 and 9-11 have been examined on the merits and stand rejected.

Claims 5-8 and 12 are withdrawn as non-elected subject matter.

The specification has amended at page 9, line 1 to correct a drafting error. The correct size of the adenovirus genome DNA is about 33-34 kb as evident from the disclosure at pages 8-9, in particular, page 9, lines 7-8.

Claims 1 and 9 have been amended to clarify the DNA size of the various components of the recombinant adenovirus vector and to clarify the method steps involved as supported by the disclosure and the original claims.

For instance, support for the "adenovirus genome DNA of about 33-34 kb" in amended claims 1 and 9 can be found in the disclosure at pages 8-9, wherein it disclosed that the adenovirus genome DNA is obtained from full length adenovirus DNA (about 36 kb) by deleting E1 (about 2 kb) or both E1 and E3 regions (about 3 kb). See also page 6, line 30 and page 9, lines 7-8.

Support for the DNA sequence of the cosmid and outer sequences of "about 7 kb" can be found in the disclosure, for example, in Fig. 1, wherein the cosmid/adenovirus vector pACL is about 41 kb whose adenovirus DNA is about 34 kb (deletion of E1 only). See also page 7, line 1. In the case of using adenovirus DNA of about 33 kb (deletion of both E1 and E3), the cosmid/adenovirus vector might be about 40 kb.

Claims 1 and 9 have been amended to clarify that the "outer sequences" of the DNA sequence are additional sequences at the outer side of the recombinase recognition sequences as supported by the disclosure, for example, at page 9, lines 19-20.

Support for "deletion site of an E1 region or both E1 and E3 regions" in claims 1 and 9 can be found in the disclosure, for example, at page 4, lines 26-27, page 6, lines 17-18 and page 9, lines 1-3.

The "recombinant adenovirus vector of about 38 kb" of amended claims 1 and 9 is exemplified in Examples 2-3 on pages 13-16. These examples describe the construction of a recombinant adenovirus vector, wherein the expression cassette (4.2 kb) was inserted into a cosmid/adenovirus vector pACL to construct a recombinant adenovirus vector of about 45 kb. Then, the cosmid sequence was deleted to construct the recombinant adenovirus vector of about 38 kb. Example 3 on pages 14-16 also shows that the obtained recombinant adenovirus vector of about 38 kb was infectious to animal cells, but the recombinant cosmid/adenovirus vector of about 45 kb was not. See also the disclosure in Example 4 at page 17, line 4 for additional support for the recombinant adenovirus vector of about 38 kb.

Therefore, no new matter has been added by this amendment.

II. INDEFINITENESS REJECTION

Claims 1-4 and 9-11 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the reasons set forth at page 3 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims.

Claims 1 and 9 have been amended to clarify that the "outer sequences" of the DNA sequence are additional sequences at the outer side of the recombinase recognition sequences as supported by the disclosure at page 9, lines 19-20. Based on this disclosure, one of skill in the art would clearly understand the metes and bounds of the term "outer sequence."

The amended claims clarify that the deletion site is an E1 region only (about 2.0 kb) or both E1 and E3 regions, including everything between E1 and E3 (about 3.0 kb), as supported by the disclosure at page 4, lines 26-27, page 6, lines 17-18 and page 9, lines 1-3.

Therefore, the rejection of claims 1-4 and 9-11 under 35 U.S.C. § 112, second paragraph, is untenable and should be withdrawn.

III. OBVIOUSNESS REJECTION

Claims 1-4 and 9-11 were rejected under 35 U.S.C. § 103(a) as obvious over Graham, in view of Fu and Chen. See pages 3-5 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims.

To establish obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. Third, the prior art must provide a reasonable expectation of success.

The amended claims call for constructing a recombinant adenovirus vector of about 38 kb comprising an adenovirus genome DNA of about 33-34 kb and an expression cassette of about 4-5 kb, which comprises: (i) constructing a recombinant cosmid/adenovirus vector of about 45 kb by inserting a DNA sequence of about 7 kb and the expression cassette of about 4-5 kb into the adenovirus genome DNA at a deletion site of an E1 region or both E1 and E3 regions of the adenovirus genome DNA, wherein the DNA sequence consists of a cosmid sequence having recombinase recognition sequences at both ends and outer sequences extended from outer sides of the recombinase recognition sequences, and at least one of the outer sequences has a cloning site for insertion of the expression cassette; (ii) cotransfecting the recombinant cosmid/adenovirus vector and a recombinase-expression vector into cells producing adenovirus E1 protein; and (iii) deleting the cosmid vector sequence from the recombinant cosmid/adenovirus vector but retaining the outer sequences therein, to produce the recombinant adenovirus vector of about 38 kb comprising the adenovirus genome DNA of about 33-34 kb and the outer sequences into which the expression cassette of about 4-5 kb is inserted.

The cited references fail to disclose or suggest each and every element of the claimed invention, namely the specific sizes of the structural components of the claimed recombinant adenovirus vector, wherein the expression cassette is inserted into the outer sequence of the DNA sequence of the vector.

Graham fails to disclose or suggest the specific sizes of the structural components of the claimed recombinant adenovirus vector. In fact, the recombinant adenovirus vector of Graham is structurally different from that of the instant invention.

As discussed in the paragraphs bridging pages 2-3 of the disclosure, the Graham reference describes a method for constructing a recombinant adenovirus vector using a circular DNA constructed by inserting a small plasmid at the restriction enzyme Xba I site, which site exists at the one location in the E1 region of the adenovirus 5 type, and then transfection to a mammalian cell line (the 293 cells). It was reported that the circular DNA produces the infectious virus. See also the Abstract on page 2917 of Graham. The report suggests that a recombinant adenovirus vector can be constructed by replacing the E1 region or E3 region of a circular adenovirus DNA with an exogenous gene.

However, when a recombinant adenovirus vector is actually constructed according to this method, two problems arise. One is the low efficiency in incorporating the expression cassette into the extremely large plasmid which contains the adenovirus genome DNA. The other problem is that the plasmid DNA portion remains in the constructed adenovirus vector. See page 4, lines 6-12 of the disclosure.

In contrast, the method of the present invention overcomes these problems in that it does not have a low efficiency of incorporating the expression cassette and it deletes the cosmid vector. The deletion of the cosmid sequence means that the result recombinant adenovirus vector does not retain the plasmid DNA portions as in Graham. Thus, the method of the present invention results in a structurally different recombinant adenovirus vector from that in Graham.

Chen also fails to disclose the structural components of the claimed adenovirus vector. This reference is relied upon for disclosing the action of different recombinases on the adenovirus genome. However, it mentions nothing regarding the insertion site of the expression cassette nor the specific structural components of the adenovirus vector of the claimed invention.

Fu describes a process for using a cosmid vector to reconstruct the whole adenovirus genome *in vitro*. However, as discussed on page 3, lines 22-25 of the instant disclosure and in the last paragraph in column 2 on page 1328 of Fu, the process in Fu is complicated and it is

difficult to obtain sufficient ligated DNA for transfection of mammalian cells to develop infectious recombinant adenoviral particles. In other words, the method in Fu is impractical.

In contrast, the instant invention overcomes these problems. Prior to the instant invention, it was known that a recombinant adenovirus vector should be about 36 kb (as compared to wild type adenovirus) to maintain the ability to infect animal cells and produce infectious virus particles. However, as evident from the Examples of the instant disclosure, the adenovirus vector of the present invention is about 38 kb and retains the ability to infect animal cells and produce infectious virus particles.

See, for instance, Example 2 on page 14, lines 10-11 of the disclosure, wherein it is described that the vector was obtained and amplified on a large scale. See also, Example 3 at line 28 to page 14, line 2 where it is disclosed that the cosmid sequence was efficiently removed to produce the circular adenovirus vector genome of 38 kb containing the expression cassette, and the infectious recombinant adenovirus vector was produced. See also Example 5 at page 18, lines 14-17, wherein it is shown that the present invention enables production of recombinant adenovirus vector of an extreme homogenous quality resulting in reliable expression by the vector. Likewise, in Example 7 at page 19, lines 17-21, it is shown that the recombinant adenovirus vector can be efficiently constructed utilizing the claimed invention.

Thus, unlike the method in the prior art, the instant invention results in an efficient process that produces a recombinant adenovirus vector which is structurally different from that in the prior art.

In view of the above, the rejection of claims 1-4 and 9-11 under 35 U.S.C. § 103(a) as obvious over Graham, Fu and Chen is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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